CHAPTER 92

Oral Solid Dosage Forms

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Drug substances most frequently are administered orally by means of solid dosage forms such as tablets and capsules. Large-scale production methods used for their preparation, as described later in the chapter, require the presence of other materials in addition to the active ingredients. Additives also may be included in the formulations to facilitate handling, enhance the physical appearance, improve stability and aid in the delivery of the drug to the bloodstream after administration. These supposedly inert ingredients, as well as the production methods employed, have been shown in some cases to influence the absorption or bioavailability of the drug substances.[1] Therefore, care must be taken in the selection and evaluation of additives and preparation methods to ensure that the drug-delivery goals and therapeutic efficacy of the active ingredient will not be diminished.

In a limited number of cases it has been shown that the drug substance's solubility and other physicochemical characteristics have influenced its physiological availability from a solid dosage form. These characteristics include its particle size, whether it is amorphous or crystalline, whether it is solvated or nonsolvated and its polymorphic form. After clinically effective formulations are obtained, such variations among dosage units of a given batch, as well as batch-to-batch differences, should be reduced to a minimum through proper in-process controls and good manufacturing practices. The recognition of the importance of validation both for equipment and processes greatly has enhanced assurance in the reproducibility of formulations. It is in these areas that significant progress has been made with the realization that large-scale production of a satisfactory tablet or capsule depends not only on the availability of a clinically effective

Fig 1. Tablet press operators checking batch record in conformance with Current Good Manufacturing Practices (courtesy. Lilly).

formulation but also on the raw materials, facilities, personnel, documentation, validated processes and equipment, packaging and the controls used during and after preparation (Fig 1).

Tablets

Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or molding methods. They have been in widespread use since the latter part of the 19th century and their popularity continues. The term *compressed tablet* is believed to have been used first by John Wyeth and Brother of Philadelphia. During this same period, molded tablets were introduced to be used as *hypodermic* tablets for the extemporaneous preparation of solutions for injection. Tablets remain popular as a dosage form because of the advantages afforded both to the manufacturer (eg, simplicity and economy of preparation, stability and convenience in packaging, shipping and dispensing) and the patient (eg, accuracy of dosage, compactness, portability, blandness of taste and ease of administration).

Although the basic mechanical approach for their manufacture has remained the same, tablet technology has undergone great improvement. Efforts are being made continually to understand more clearly the physical characteristics of powder compaction and the factors affecting the availability of the

drug substance from the dosage form after oral administration. Tableting equipment continues to improve both as to production speed and the uniformity of tablets compressed. Recent advances in tablet technology have been reviewed.[2-13]

Although tablets frequently are discoid in shape, they also may be round, oval, oblong, cylindrical or triangular. They may differ greatly in size and weight depending on the amount of drug substance present and the intended method of administration. They are divided into two general classes, whether they are made by compression or molding. Compressed tablets usually are prepared by large-scale production methods, while molded tablets generally involve small-scale operations. The various tablet types and abbreviations used in referring to them are listed below.

Compressed Tablets (CT)

These tablets are formed by compression and contain no special coating. They are made from powdered, crystalline or granular materials, alone or in combination with binders, disintegrants, controlled-release polymers, lubricants, diluents and, in many cases, colorants.

Sugar-Coated Tablets (SCT)—These are compressed tablets containing a sugar coating. Such coatings may be colored and are beneficial in covering up drug substances possessing objectionable tastes or odors, and in protecting materials sensitive to oxidation.

Film-Coated Tablets (FCT)—These are compressed tablets which are covered with a thin layer or film of a water-soluble material. A number of polymeric substances with film-forming properties may be used. Film coating imparts the same general characteristics as sugar coating with the added advantage of a greatly reduced time period required for the coating operation.

Enteric-Coated Tablets (ECT)—These are compressed tablets coated with substances that resist solution in gastric fluid but disintegrate in the intestine. Enteric coatings can be used for tablets containing drug substances which are inactivated or destroyed in the stomach, for those which irritate the mucosa or as a means of delayed release of the medication.

Multiple Compressed Tablets (MCT)—These are compressed tablets made by more than one compression cycle.

Layered Tablets—Such tablets are prepared by compressing additional tablet granulation on a previously compressed granulation. The operation may be repeated to produce multilayered tablets of two or three layers. Special tablet presses are required to make layered tablets such as the Versa press (*Stokes/Pennwalt*).

Press-Coated Tablets—Such tablets, also referred to as dry-coated, are prepared by feeding previously compressed tablets into a special tableting machine and compressing another granulation layer around the preformed tablets. They have all the advantages of compressed tablets, ie, slotting, monogramming, speed of disintegration, etc, while retaining the attributes of sugar-coated tablets in masking the taste of the drug substance in the core tablets. An example of a press-coated tablet press is the *Manesty* Drycota. Press-coated tablets also can be used to separate incompatible drug substances; in addition, they can provide a means to give an enteric coating to the core tablets. Both types of multiple-compressed tablets have been used widely in the design of prolonged-action dosage forms.

Controlled-Release Tablets—Compressed tablets can be formulated to release the drug slowly over a prolonged period of time. Hence, these dosage forms have been referred to as *Prolonged-Release* or *Sustained-Release* dosage forms as well. These tablets (as well as capsule versions) can be categorized into three types: (1) those which respond to some physiological condition to release the drug, such as enteric coatings; (2) those that release the drug in a relatively steady, controlled manner and (3) those that combine combinations of mechanisms to release "pulses" of drug, such as repeat-action tablets. The performance of these systems are described in more detail in Chapter 94.

Tablets for Solution—Compressed tablets to be used for preparing solutions or imparting given characteristics to solutions must be labeled to indicate that they are not to be swallowed. Examples of these tablets are Halazone Tablets for Solution and Potassium Permanganate Tablets for Solution.

Effervescent Tablets—In addition to the drug substance, these contain sodium bicarbonate and an organic acid such as tartaric or citric. In the presence of water, these additives react liberating carbon dioxide which acts as a disintegrator and produces effervescence. Except for small quantities of lubricants present, effervescent tablets are soluble.

Compressed Suppositories or Inserts—Occasionally, vaginal suppositories, such as Metronidazole Tablets, are prepared by compression. Tablets for this use usually contain lactose as the diluent. In this case, as well as for any tablet intended for administration other than by swallowing, the label must indicate the manner in which it is to be used.

Buccal and Sublingual Tablets—These are small, flat, oval tablets. Tablets intended for buccal administration by inserting into the buccal pouch may dissolve or erode slowly; therefore, they are formulated and compressed with sufficient pressure to give a hard tablet. Progesterone Tablets may be administered in this way.

Some newer approaches use tablets that melt at body temperatures. The matrix of the tablet is solidified while the drug is in solution. After melting, the drug is automatically in solution and available for absorption, thus eliminating dissolution as a rate-limiting step in the absorption of poorly soluble compounds. Sublingual tablets, such as those containing nitroglycerin, isoproterenol hydrochloride or erythrityl tetranitrate, are placed under the tongue. Sublingual tablets dissolve rapidly and the drug substances are absorbed readily by this form of administration.

Molded Tablets or Tablet Triturates (TT)

Tablet triturates usually are made from moist material using a triturate mold which gives them the shape of cut sections of a cylinder. Such tablets must be completely and rapidly soluble. The problem arising from compression of these tablets is the failure to find a lubricant that is completely water soluble.

Dispensing Tablets (DT)—These tablets provide a convenient quantity of potent drug that can be incorporated readily into powders and liquids, thus circumventing the necessity to weigh small quantities. These tablets are supplied primarily as a convenience for extemporaneous compounding and should never be dispensed as a dosage form.

Hypodermic Tablets (HT)—Hypodermic tablets are soft, readily soluble tablets and originally were used for the preparation of solutions to be injected. Since stable parenteral solutions are now available for most drug substances, there is no justification for the use of hypodermic tablets for injection. Their use in this manner should be discouraged since the resulting solutions are not sterile. Large quantities of these tablets continue to be made, but for oral administration. No hypodermic tablets ever have been recognized by the official compendia.

Compressed Tablets (CT)

In order for medicinal substances, with or without diluents, to be made into solid dosage forms with pressure, using available equipment, it is necessary that the material, either in crystalline or powdered form, possess a number of physical characteristics. These characteristics include the ability to flow freely, cohesiveness and lubrication. The ingredients such as disintegrants designed to break the tablet up in gastrointestinal fluids, and controlled-release polymers designed to slow down drug release, ideally should possess these characteristics, or not interfere with the desirable performance traits of the other excipients. Since most materials have none or only some of these properties, methods of tablet formulation and preparation have been developed to impart these desirable characteristics to the material which is to be compressed into tablets.

The basic mechanical unit in all tablet-compression equipment includes a lower punch which fits into a die from the bottom and an upper punch, having a head of the same shape and dimensions, which enters the die cavity from the top after the tableting material fills the die cavity (see Fig 2). The tablet is formed by pressure applied on the punches and subsequently is ejected from the die. The weight of the tablet is determined by the volume of the material which fills the die cavity. Therefore, the ability of the granulation to flow freely into the die is important in insuring a uniform fill, as well as the continuous movement of the granulation from the source of supply or feed hopper. If the tablet granulation does not possess cohesive properties, the tablet after compression will crumble and fall apart on handling. As the punches must move freely within the die and the tablet must be ejected readily from the punch faces, the material must have a degree of lubrication to minimize friction and allow for the removal of the compressed tablets.

There are three general methods of tablet preparation: the wet-granulation method, the dry-granulation method and di-
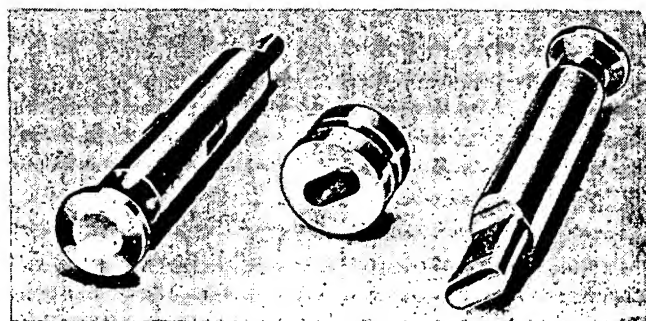

Fig 2. Basic mechanical unit for tablet compression: lower punch, die and upper punch (courtesy, Vector/Colton).

rect compression.   The method of preparation and the added ingredients are selected in order to give the tablet formulation the desirable physical characteristics allowing the rapid compression of tablets.   After compression, the tablets must have a number of additional attributes such as appearance, hardness, disintegration ability, appropriate dissolution characteristics and uniformity which also are influenced both by the method of preparation and by the added materials present in the formulation.   In the preparation of compressed tablets, the formulator also must be cognizant of the effect which the ingredients and methods of preparation may have on the availability of the active ingredients and, hence, the therapeutic efficacy of the dosage form.   In response to a request by physicians to change a dicumarol tablet in order that it might be broken more easily, a Canadian company reformulated to make a large tablet with a score.   Subsequent use of the tablet, containing the same amount of drug substance as the previous tablet, resulted in complaints that larger-than-usual doses were needed to produce the same therapeutic response. On the other hand, literature reports indicate that the reformulation of a commercial digoxin tablet resulted in a tablet, although containing the same quantity of drug substance, that gave the desired clinical response at half its original dose. Methods and principles that can be used to assess the effects of excipients and additives on drug absorption have been reviewed.[2,14,15]   See Chapters 35, 42 and 83.

Tablet Ingredients

In addition to the active or therapeutic ingredient, tablets contain a number of inert materials.   The latter are known as additives or *excipients*.   They may be classified according to the part they play in the finished tablet.   The first group contains those which help to impart satisfactory processing and compression characteristics to the formulation.   These include diluents, binders, glidants and lubricants.   The second group of added substances helps to give additional desirable physical characteristics to the finished tablet.   Included in this group are disintegrants, colors, and in the case of chewable tablets, flavors and sweetening agents, and in the case of controlled-release tablets, polymers or waxes or other solubility-retarding materials.

Although the term *inert* has been applied to these added materials, it is becoming increasingly apparent that there is an important relationship between the properties of the excipients and the dosage forms containing them.   Preformulation studies demonstrate their influence on stability, bioavailability and the processes by which the dosage forms are prepared. The need for acquiring more information and use standards for excipients has been recognized in a joint venture of the Academy of Pharmaceutical Sciences and the Council of the Pharmaceutical Society of Great Britain.   The result is called the *Handbook of Pharmaceutical Excipients*.   This reference now is distributed widely throughout the world.[16]

Diluents

Frequently, the single dose of the active ingredient is small and an inert substance is added to increase the bulk in order to make the tablet a practical size for compression.   Compressed tablets of dexamethasone contain 0.75 mg steroid per tablet; hence, it is obvious that another material must be added to make tableting possible.   Diluents used for this purpose include dicalcium phosphate, calcium sulfate, lactose, cellulose, kaolin, mannitol, sodium chloride, dry starch and powdered sugar.   Certain diluents, such as mannitol, lactose, sorbitol, sucrose and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such tablets commonly are called *chewable tablets*.   Upon chewing, properly prepared tablets will disintegrate smoothly at a satisfactory rate, have a pleasant taste and feel and leave no unpleasant aftertaste in the mouth.   Diluents used as excipients for direct compression formulas have been subjected to prior

processing to give them flowability and compressibility.   These are discussed under *Direct Compression*, page 1626.

Most formulators of immediate-release tablets tend to use consistently only one or two diluents selected from the above group in their tablet formulations.   Usually, these have been selected on the basis of experience and cost factors. However, in the formulation of new therapeutic agents, the compatibility of the diluents with the drug must be considered, eg, calcium salts used as diluents for the broad-spectrum antibiotic tetracycline have been shown to interfere with the drug's absorption from the gastrointestinal tract.   When drug substances have low water solubility, it is recommended that water-soluble diluents be used to avoid possible bioavailability problems.   Highly adsorbent substances, eg, bentonite and kaolin, are to be avoided in making tablets of drugs used clinically in small dosage, such as the cardiac glycosides, alkaloids and the synthetic estrogens.   These drug substances may be adsorbed after administration.   The combination of amine bases with lactose, or amine salts with lactose in the presence of an alkaline lubricant, results in tablets which discolor on aging.

Microcrystalline cellulose (Avicel) usually is used as an excipient in direct-compression formulas.   However, its presence in 5 to 15% concentrations in wet granulations has been shown to be beneficial in the granulation and drying processes in minimizing case-hardening of the tablets and in reducing tablet mottling.

Many ingredients are used for several different purposes, even within the same formulation; eg, corn starch can be used in paste form as a binder.   When added in drug or suspension form, it is a good disintegrant.   Even though these two uses are to achieve opposite goals, some tablet formulas use corn starch in both ways.   In some controlled-release formulas, the polymer hydroxypropylmethylcellulose (HPMC) is used both as an aid to prolong the release from the tablet, as well as a film-former in the tablet coating.   Therefore, most excipients used in formulating tablets and capsules have many uses, and a thorough understanding of their properties and limitations is necessary in order to use them rationally.

Binders

Agents used to impart cohesive qualities to the powdered material are referred to as binders or granulators.   They impart a cohesiveness to the tablet formulation which insures the tablet remaining intact after compression, as well as improving the free-flowing qualities by the formulation of granules of desired hardness and size.   Materials commonly used as binders include starch, gelatin and sugars as sucrose, glucose, dextrose, molasses and lactose.   Natural and synthetic gums which have been used include acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, Veegum and larch arabogalactan.   Other agents which may be considered binders under certain circumstances are polyethylene glycol, ethylcellulose, waxes, water and alcohol.

The quantity of binder used has considerable influence on the characteristics of the compressed tablets.   The use of too much binder or too strong a binder will make a hard tablet which will not disintegrate easily and which will cause excessive wear of punches and dies.   Differences in binders used for CT Tolbutamide resulted in differences in hypoglycemic effects observed clinically.   Materials which have no cohesive qualities of their own will require a stronger binder than those with these qualities.   Alcohol and water are not binders in the true sense of the word, but because of their solvent action on some ingredients such as lactose, starch and celluloses, they change the powdered material to granules and the residual moisture retained enables the materials to adhere together when compressed.

Binders are used both as a solution and in a dry form depending on the other ingredients in the formulation and the method of preparation.   However, several *pregelatinized*

starches available are intended to be added in the dry form so that water alone can be used as the granulating solution. The same amount of binder in solution will be more effective than if it were dispersed in a dry form and moistened with the solvent. By the latter procedure, the binding agent is not as effective in reaching and wetting each of the particles within the mass of powders. Each of the particles in a powder blend has a coating of adsorbed air on its surface, and it is this film which must be penetrated before the powders can be wetted by the binder solution. After wetting, a certain period of time is necessary to dissolve the binder completely and make it completely available for use. Since powders differ with respect to the ease with which they can be wetted, and their rate of solubilization, it is preferable to incorporate the binding agent in solution. By this technique it often is possible to gain effective binding with a lower concentration of binder.

The direct-compression method for preparing tablets (see page 1630) requires a material that not only is free-flowing but also sufficiently cohesive to act as a binder. This use has been described for a number of materials including microcrystalline cellulose, microcrystalline dextrose, amylose and polyvinylpyrrolidone. It has been postulated that microcrystalline cellulose is a special form of cellulose fibril in which the individual crystallites are held together largely by hydrogen bonding. The disintegration of tablets containing the cellulose occurs by breaking the intercrystallite bonds by the disintegrating medium.

Starch Paste—Corn starch is used widely as a binder. The concentration may vary from 10 to 20%. It usually is prepared as it is to be used by dispersing corn starch in sufficient cold purified water to make a 5 to 10% w/w suspension and warming in a water bath with continuous stirring until a translucent paste forms. It has been observed that during paste formation, not all of the starch is hydrolyzed. Starch paste then, is not only useful as a binder, but also as a method to incorporate some disintegrant inside the granules.

Gelatin Solution—Gelatin generally is used as a 10 to 20% solution; gelatin solutions should be prepared freshly as needed and used while warm or they will solidify. The gelatin is added to cold purified water and allowed to stand until it is hydrated. It then is warmed in a water bath to dissolve the gelatin, and the solution is made up to the final volume on a weight basis to give the concentration desired.

Cellulosic Solutions—Various cellulosics have been used as binders in solution form. Hydroxypropylmethylcellulose (HPMC) has been used widely in this regard. Typical of a number of cellulosics, HPMC is more soluble in cold water than hot. It also is more dispersable in hot water than cold. Hence, in order to obtain a good, smooth gel that is free from lumps or "fisheyes," it is necessary to add the HPMC in hot, almost boiling water and, under agitation, cool the mixture down as quickly as possible, as low as possible. Other water-soluble cellulosics such as hydroxyethylcellulose (HEC) and hydroxypropylcellulose (HPC) have been used successfully in solution as binders.

Not all cellulosics are soluble in water. Ethylcellulose can be used effectively when dissolved in alcohol, or as a dry binder which then is wetted with alcohol. It is used as a binder for materials that are moisture-sensitive.

Polyvinylpyrrolidone—PVP can be used as an aqueous or alcoholic solution and this versatility has increased its popularity. Concentrations range from 2% and vary considerably.

It will be noted that binder solutions usually are made up to weight rather than volume. This is to enable the formulator to determine the weight of the solids which have been added to the tablet granulation in the binding solution. This becomes part of the total weight of the granulation and must be taken into consideration in determining the weight of the compressed tablet, which will contain the stated amount of the therapeutic agent.

As can be seen by the list of binders in this chapter, most modern binders used in solution are polymeric in form. Because of this, the flow or spreadability of these solutions becomes important when selecting the appropriate granulating equipment. The rheology of polymeric solutions is a fascinating subject in and of itself, and should be considered for these materials.

Lubricants

Lubricants have a number of functions in tablet manufacture. They prevent adhesion of the tablet material to the surface of the dies and punches, reduce interparticle friction, facilitate the ejection of the tablets from the die cavity and may improve the rate of flow of the tablet granulation. Commonly used lubricants include talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils and polyethylene glycol (PEG). Most lubricants, with the exception of talc, are used in concentrations less than 1%. When used alone, talc may require concentrations as high as 5%. Lubricants are in most cases hydrophobic materials. Poor selection or excessive amounts can result in "waterproofing" the tablets, resulting in poor tablet disintegration and/or delayed dissolution of the drug substance.

The addition of the proper lubricant is highly desirable if the material to be tableted tends to stick to the punches and dies. Immediately after compression, most tablets have the tendency to expand and will bind and stick to the side of the die. The choice of the proper lubricant effectively will overcome this.

The method of adding a lubricant to a granulation is important if the material is to perform its function satisfactorily. The lubricant should be divided finely by passing it through a 60- to 100-mesh nylon cloth onto the granulation. In production this is called *bolting* the lubricant. After adding the lubricant, the granulation is tumbled or mixed gently to distribute the lubricant without coating the particles too well or breaking them down to finer particles. Some research has concluded that the order of mixing of lubricants and other excipients can have a profound effect on the performance of the final dosage form. Thus, attention to the mixing process itself is just as important as the selection of lubricant materials.

These process variables can be seen in the prolonged blending of a lubricant in a granulation. Overblending materially can affect the hardness, disintegration time and dissolution performance for the resultant tablets.

The quantity of lubricant varies, being as low as 0.1%, and in some cases as high as 5%. Lubricants have been added to the granulating agents in the form of suspensions or emulsions. This technique serves to reduce the number of operational procedures and thus reduce the processing time.

In selecting a lubricant, proper attention must be given to its compatibility with the drug agent. Perhaps the most widely investigated drug is acetylsalicylic acid. Different talcs varied significantly the stability of aspirin. Talc with a high calcium content and a high loss on ignition was associated with increased aspirin decomposition. From a stability standpoint, the relative acceptability of tablet lubricants for combination with aspirin was found to decrease in the following order: hydrogenated vegetable oil, stearic acid, talc and aluminum stearate.

The primary problem in the preparation of a water-soluble tablet is the selection of a satisfactory lubricant. Soluble lubricants reported to be effective include sodium benzoate, a mixture of sodium benzoate and sodium acetate, sodium chloride, leucine and Carbowax 4000. However, it has been suggested that formulations used to prepare water-soluble tablets may represent a number of compromises between compression efficiency and water solubility. While magnesium stearate is one of the most widely used lubricants, its hydrophobic properties can retard disintegration and dissolution. To overcome these waterproofing characteristics, sodium lauryl sulfate sometimes is included. One compound found to have the lubricating properties of magnesium stearate without its disadvantages is magnesium lauryl sulfate. Its safety for use in pharmaceuticals has not been established.

Glidants

A glidant is a substance which improves the flow characteristics of a powder mixture. These materials always are added in the dry state just prior to compression (ie, during the lubrication step). Colloidal silicon dioxide [Cab-o-sil (*Cabot*)] is the most commonly used glidant and generally is used in low concentrations of 1% or less. Talc (asbestos-free) also is used and may serve the dual purpose as lubricant/glidant.

It is especially important to optimize the order of addition and the mixing process for these materials in order to maximize their effect and to make sure that their influence on the lubricant(s) is minimized.

Disintegrants

A disintegrant is a substance, or a mixture of substances, added to a tablet to facilitate its breakup or disintegration after administration. The active ingredient must be released from the tablet matrix as efficiently as possible to allow for its rapid dissolution. Materials serving as disintegrants have been classified chemically as starches, clays, celluloses, algins, gums and cross-linked polymers.

The oldest and still the most popular disintegrants are corn and potato starch which have been well-dried and powdered. Starch has a great affinity for water and swells when moistened, thus facilitating the rupture of the tablet matrix. However, others have suggested that its disintegrating action in tablets is due to capillary action rather than swelling; the spherical shape of the starch grains increases the porosity of the tablet, thus promoting capillary action. Starch, 5%, is suggested, but if more rapid disintegration is desired, this amount may be increased to 10 or 15%. Although it might be expected that disintegration time would decrease as the percentage of starch in the tablet increased, this does not appear to be the case for tolbutamide tablets. In this instance, there appears to be a critical starch concentration for different granulations of the chemical. When their disintegration effect is desired, starches are added to the powder blends in the dry state.

A group of materials known as *super disintegrants* have gained in popularity as disintegrating agents. The name comes from the low levels (2 to 4%) at which they are completely effective. Croscarmelose, crospovidone and sodium starch glycolate represent examples of a cross-linked cellulose, a cross-linked polymer and a cross-linked starch, respectively.

The development of these disintegrants fostered new theories about the various mechanisms by which disintegrants work. Sodium starch glycolate swells 7- to 12-fold in less than 30 seconds. Croscarmelose swells 4- to 8-fold in less than 10 seconds. The starch swells equally in all three dimensions, while the cellulose swells only in two dimensions, leaving fiber length essentially the same. Since croscarmelose is the more efficient disintegrating agent, it is postulated that the rate, force and extent of swelling play an important role in those disintegrants that work by swelling. Cross-linked PVP swells little, but returns to its original boundaries quickly after compression. Wicking, or capillary action, also is postulated to be a major factor in the ability of cross-linked PVP to function.[17-19]

In addition to the starches, a large variety of materials have been used and are reported to be effective as disintegrants. This group includes Veegum HV, methylcellulose, agar, bentonite, cellulose and wood products, natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethylcellulose.[20] Sodium lauryl sulfate in combination with starch also has been demonstrated to be an effective disintegrant. In some cases the apparent effectiveness of surfactants in improving tablet disintegration is postulated as being due to an increase in the rate of wetting.

The disintegrating agent usually is mixed with the active ingredients and diluents prior to granulation. In some cases it may be advantageous to divide the starch into two portions: one part is added to the powdered formula prior to granulation, and the remainder is mixed with the lubricant and added prior to compression. Incorporated in this manner, the starch serves a double purpose; the portion added to the lubricant rapidly breaks down the tablet to granules, and the starch mixed with the active ingredients disintegrates the granules into smaller particles. Veegum has been shown to be more effective as a disintegrator in sulfathiazole tablets when most of the quantity is added after granulation and only a small amount before granulation. Likewise, the montmorillonite clays were found to be good tablet disintegrants when added to prepared granulations as powder. They are much less effective as disintegrants when incorporated within the granules.

Factors other than the presence of disintegrants can affect significantly the disintegration time of compressed tablets. The binder, tablet hardness and the lubricant have been shown to influence the disintegration time. Thus, when the formulator is faced with a problem concerning the disintegration of a compressed tablet, the answer may not lie in the selection and quantity of the disintegrating agent alone.

The evolution of carbon dioxide is also an effective way to cause the disintegration of compressed tablets. Tablets containing a mixture of sodium bicarbonate and an acidulant such as tartaric or citric acid will effervesce when added to water. Sufficient acid is added to produce a neutral or slightly acidic reaction when disintegration in water is rapid and complete. One drawback to the use of the effervescent type of disintegrator is that such tablets must be kept in a dry atmosphere at all times during manufacture, storage and packaging. Soluble, effervescent tablets provide a popular form for dispensing aspirin and noncaloric sweetening agents.

Coloring Agents

Colors in compressed tablets serve functions other than making the dosage form more esthetic in appearance. Color helps the manufacturer to control the product during its preparation, as well as serving as a means of identification to the user. The wide diversity in the use of colors in solid dosage forms makes it possible to use color as an important category in the identification code developed by the AMA to establish the identity of an unknown compressed tablet in situations arising from poisoning.

All colorants used in pharmaceuticals must be approved and certified by the FDA. For several decades colorants have been subjected to rigid toxicity standards and, as a result, a number of colorants have been removed from an approved list of FD&C colors or "delisted." Several have been listed as well. The colorants currently approved in the US are listed in Table 1. Each country has its own list of approved colorants, and formulators must consider this in designing products for the international market.[21]

Any of the approved certified water-soluble FD&C dyes, mixtures of the same or their corresponding lakes may be used to color tablets. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal resulting in an insoluble form of the dye. In some instances multiple dyes are used to give a purposefully heterogeneous coloring in the form of speckling to compressed tablets. The dyes available do not meet all the criteria required for the ideal pharmaceutical colorants. The photosensitivity of several of the commonly used colorants and their lakes has been investigated, as well as the protection afforded by a number of glasses used in packaging tablets.

Another approach for improving the photostability of dyes has been in the use of ultraviolet-absorbing chemicals in the tablet formulations with the dyes. The Di-Pac line (*Am star*) is a series of commercially available colored, direct-compression sugars.

The most common method of adding color to a tablet formulation is to dissolve the dye in the binding solution prior to the granulating process. Another approach is to adsorb the dye

Table 1—Colors Approved for Use in the US in Oral Dosage Forms[a,b]

Color	Other names	Color Index (CI 1971)	Use restriction (US)
FD & C Red 40	Allura red	16035	FDA certification on each lot of dye
D & C Red 33	Acid fuchsin D Naphtalone red B	17200	ADI 0–0.76 mg.
D & C Red 36			ADI 0—1.0 mg
Canthaxanthinin	Food orange 8	40850	None
D & C Red 22	Eosin Y	45380	FDA certification on each lot of dye
D & C Red 28	Phloxine B	45410	FDA certification on each lot of dye
D & C Red 3	Erythrosine	45430	FDA certification on each lot of dye
Cochineal extract	Natural red 4 Carmine	75470	None
Iron oxide—red	—	77491	ADI 0–5 mg elemental iron
FD & C Yellow 6	Sunset yellow FCF Yellow orange 5	15985	None
FD & C Yellow 5	Tartrazine	19140	Label declaration and FDA certification on each lot of dye
D & C Yellow 10	Quinoline yellow WS	47005	FDA certification on each lot of dye
Beta-carotene	—	40800	
Iron oxide—yellow	—	77492	ADI 0–5 mg elemental iron
FD & C Blue 1	Brilliant blue FCF	42090	FDA certification on each lot of dye
FD & C Blue 2	Indigotine Indigo carmine	73015	None
FD & C Green 3	Fast green FCF	42035	FDA certification on each lot of dye
Iron oxide—black	—	77499	ADI 0–5 mg elemental iron
Caramel	Burnt sugar	—	None
Titanium dioxide	—	77891	None

[a] Abbreviations: ADI—Acceptable Daily Intake (per kg body weight)
  CI— Color index numbers of 1971 (US)
  D & C— Drug and Cosmetic Dyes (US)

FD & C— Food, Drug and Cosmetic Dyes (US)
FDA—Food and Drug Administration (US)
[b] As of February, 1988 and subject to revision.

on starch or calcium sulfate from its aqueous solution; the resultant powder is dried and blended with the other ingredients. If the insoluble lakes are used, they may be blended with the other dry ingredients. Frequently during drying, colors in wet granulations migrate, resulting in an uneven distribution of the color in the granulation. After compression, the tablets will have a mottled appearance due to the uneven distribution of the color. Migration of colors may be reduced by drying the granulation slowly at low temperatures and stirring the granulation while it is drying. The affinity of several water-soluble anionic certified dyes for natural starches has been demonstrated; in these cases this affinity should aid in preventing color migration.

Other additives have been shown to act as dye-migration inhibitors. Tragacanth (1%), acacia (3%), attapulgite (5%) and talc (7%) were effective in inhibiting the migration of FD&C Blue No 1 in lactose. In using dye lakes, the problem of color migration is avoided since the lakes are insoluble. Prevention of mottling can be helped also by the use of lubricants and other additives which have been colored similarly to the granulation prior to their use. The problem of mottling becomes more pronounced as the concentration of the colorants increases. Color mottling is an undesirable characteristic common to many commercial tablets.

Flavoring Agents

In addition to the sweetness which may be afforded by the diluent of the chewable tablet, eg, mannitol or lactose, artificial sweetening agents may be included. Formerly, the cyclamates, either alone or in combination with saccharin, were used widely. With the banning of the cyclamates and the indefinite status of saccharin, new natural sweeteners are being sought. Aspartame (Searle), has found applications for pharmaceutical formulations. Sweeteners other than the sugars have the advantage of reducing the bulk volume, considering the quantity of sucrose required to produce the same degree of sweetness. Being present in small quantities, they do not affect markedly the physical characteristics of the tablet granulation.

Powder Compaction

Compressed tablets became a commercially viable and efficient dosage form with the invention of tablet machines. In 1843 William Brockendon, a British inventor, author, artist and watchmaker, received British Patent #9977 for "Shaping Pills, Lozenges, and Black Lead by Pressure in Dies."[22] In over 150 years of tablet manufacture, the basic process has not changed. Surprisingly, improvements have been made only with regards to speed of manufacture and quality control.

The process of compaction has several identifiable phases. As can be seen in Fig 3, when powders undergo compression (a reduction in volume), the first process to occur is a consolidation of the powders. During this consolidation phase, the powder particles adopt a more efficient packing order. The second phase of the compaction process is elastic, or reversible deformation. If the force were to be removed during this phase, the powder would recover completely to the efficiently packed state. For most pharmaceutical powders, this phase is very short in duration, and very difficult to identify on most instrumented tablet presses. The third phase of compaction
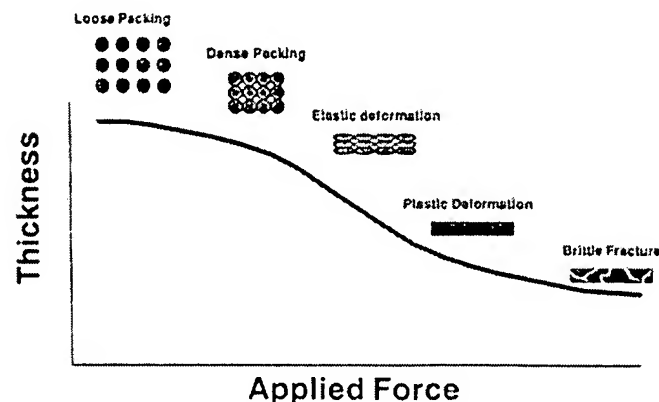
Fig 3. The stages of powder compaction.